ABSTRACT OF THE DISCLOSURE

This invention relates to a novel gene that shows tissue specific expression and increased expression in a low calcium concentration medium. Low renin hypertension is characterized by decreased levels of serum ionized calcium in the presence of increased levels of parathyroid hormone. It is hypothesized that hypertensive factor(s) are co-secreted with PTH in SHR, a model of low renin hypertension, the parathyroid hypertensive factor being one of them. As a negative calcium balance is present in spontaneously hypertensive rats (SHR), we searched for gene(s) involved in this dysregulation. A cDNA library was constructed from the SHR parathyroid gland which is a key regulator of serum ionized calcium. From 7 overlapping DNA fragments, a 1100-bp novel cDNA containing an open reading frame of 224 codons was reconstituted. This novel gene, named *HCaRG* (Hypertension-related, Calcium-regulated Gene), was negatively regulated by extracellular calcium concentration and its basal mRNA levels were higher in hypertensive animals. The deduced protein showed no transmembrane domain, 67% a helix content, a mutated calcium-binding site (EF-hand motif), 4 putative 'leucine zipper' motifs and a nuclear receptor-binding domain. At the subcellular level, *HCaRG* had a nuclear localization. We cloned the human homolog of this gene. Sequence comparison revealed 80% homology between rats and humans at the nucleotide and amino acid sequences. Tissue distribution showed a preponderance in the heart, stomach, jejunum, kidney (tubular fraction), liver and adrenal gland (mainly in the medulla). *HCaRG* mRNA was significantly more expressed in adult than in fetal organs, and its levels were decreased in tumors and cancerous cell lines. We observed that after 60-min ischemia followed by reperfusion, *HCaRG* mRNA declined rapidly in contrast with an increase in *c-myc* mRNA. Its levels then rose steadily to exceed baseline at 48 h of reperfusion. HEK293 cells stably transfected with *HCaRG* exhibited much lower proliferation, as shown by cell count and 3 H-thymidine incorporation. Taken together, our results suggest that *HCaRG* is a nuclear protein potentially involved in the control of cell proliferation.